44. (Amended) the vaccine of claim 41 which is [administered by] formulated for subcutaneous injection.

REMARKS

Double Patenting Rejections

Claims 34, 35 and 38-44 stand rejected as being unpatentably obvious over claims 1-4 of U.S. Patent No. 5,849,305, claim 5 of U.S. Patent No. 5,824,525 and claims 13-16 of U.S. Patent No. 5,587,305. Claim 40 is rejected under 35 U.S.C. §101 as claiming the same invention of claim 12 of U.S. Patent No. 5,587,305.

To advance prosecution, a terminal disclaimer is being filed to overcome the obviousness-type double patenting rejection. Applicants disagree, however, with the assertion that claim 40, directed to a vaccine comprising *P. haemolytica* ATCC 55518, claims the same invention as issued claim 12 of U.S. Patent No. 5,587,305, directed to *P. haemolytica* ATCC 55518. These claims clearly differ in scope. For example, a claim which adds the limitation of containing an adjuvant would further limit the subject matter of claim 40, but would fail to further limit the subject matter of issued claim 12. Applicants submit that the statutory double patenting rejection is improper and request the withdrawal thereof.

Section 112, second paragraph rejection

Claims 38, 39, 43 and 44 are rejected under 35 U.S.C. §112, second paragraph.

Claims 38, 39, 43 and 44 have been amended to overcome this rejection. It is respectfully submitted that these claims are now clear and properly dependent. Withdrawal is requested.

Section 112, first paragraph rejection

Claims 34, 35 and 38-50 stand rejected under 35 U.S.C. §112, first paragraph as enabled only for site-directed mutations of *aroA, PhaI,* leukotoxin operon, and neuraminidase genes, and specific

compositions for the treatment of cattle and sheep. It is respectfully noted that claims 34, 35, 38-50 are limited by virtue of the amendment filed July 19, 1999 to the subject matter which the rejection states is enabled. The maintenance of this rejection in view of the narrowed scope of the claims is not understood. Clarification is requested.

Applicants were the first to genetically modify the DNA of *P. haemolytica*. The specification teaches a method of creating a mutation in the wild-type *P. haemolytica* DNA. While techniques for the genetic modification of other bacteria have heretofore been known, prior to the present invention transformation of *P. haemolytica* had been unsuccessful due to its restriction system. Applicants' disclosure teaches the skilled artisan for the first time how to reintroduce and establish *in vitro* generated mutations into *P. haemolytica*. The invention is clearly entitled to the breadth of the claims as recited. The subject invention represents a valuable and patentable contribution to the art, and one that is entitled to broad protection. Reconsideration is requested.

Rejection over the Homchampa *et al.* reference

Claims 34-35, 38, 39, 41-44 stand rejected under 103(a) as being unpatentable over Homchampa *et al.* This rejection is respectfully traversed.

At the time the invention was made there existed a barrier to transformation in *P. haemolytica* and an expectation of negative transformation results. One skilled in the art at the time the invention was made would not have been able to use the techniques taught by Homchampa *et al.* to create an *aroA* gene mutant of *P. haemolytica* by insertion of a kanamycin-resistance gene into the *aroA* gene because of the barrier to the introduction of foreign or exogenous DNA into the bacterium, *P. haemolytica.*

It was not possible, for example, to introduce or establish foreign or exogenous DNA into *P. haemolytica* before this invention was made. The invention identifies and discloses methods to

overcome that barrier. The barrier to transformation, as discovered by applicants, was a newly discovered restriction-modification system, the *PhaI* system, present in *P. haemolytica*. This invention identifies the barrier to transformation and, more importantly, discloses methods to overcome the barrier. Only after this barrier is overcome by methods disclosed in this invention could one skilled in the art utilize standard recombinant DNA techniques to genetically modify *P. haemolytica*.

Applicants also repeat, and incorporate herein, the arguments set forth in the previous response regarding the Homchampa *et al.* reference, which arguments the examiner failed to address in the Office Action. Applicants request that the arguments be addressed so that the maintenance of the rejection can be understood and meaningful progress toward overcoming the rejection can be made.

Rejection over the Gentry *et al.* reference

Claims 34, 38, 39, 46-49 are rejected under 35 U.S.C. §102(b) as being anticipated by Gentry *et al.* Gentry *et al.* is cited by the examiner as disclosing strains of *P. haemolytica* which produce various degrees of toxicity when administered to cattle. It is the the Patent and Trademark Office's position that the variation evidenced by each of the five strains is indicative of difference in the genetic make-up of each of the leukotoxins and therefore the strains represent naturally occurring mutant *P. haemolytica* strains. Applicants respectfully disagree that the teachings of Gentry *et al.* as they would be understood by one of ordinary skill in the art anticipate the claimed invention.

Gentry *et al.* does not anticipate the invention because it does not teach or suggest that the differences found between the five strains studied were due to the genetic make-up of the leukotoxin genes. Gentry compared single strains of five different *P. haemolytica* serotypes (S1, S2, S5, S6 and S9) to an untypable (UT) strain in an attempt to detect differences which might be related to

virulence and prevalence. Gentry teaches that when injected into the lungs of healthy cattle, the lesion scores produced by the S1, S2, S5, S6 and S9 far exceeded those produce by the UT strain, which produced only minimal lung lesions. Page 362, lines 3-6. Gentry *et al.*, however, does not attribute this to the genetic make-up of the leukotoxin of the strains. Rather, it teaches away from this conclusion. Specifically, Gentry states that the UT strain's "inability to produce lesions *in vivo* may have been due to a deficiency in some pathogenic parameter other than leukotoxin production." Page 367, lines 12-15, emphasis added. Gentry reaches this conclusion because the UT strain was as toxic in the *in vitro* assay as the other strains. Page 362, line 12.

Gentry concluded that subtle differences in growth rates or the ability to maintain stationary phase of growth *in vitro* may present a selective disadvantage of certain strains of *P. haemolytica* for disease production. Sentences spanning pages 364-365. Thus Gentry attributes differential pathogenicity to growth characteristics, not to the genetic make-up of the leukotoxins.

Gentry simply fails to disclose or suggest the claimed vaccines comprising leukotoxin mutants. Gentry does not teach or deisclose leukotoxin mutant strains. Reconsideration and withdrawal is requested.

Rejection over the Cruz *et al.* reference

Claims 34, 38, 39, 47 are rejected under 35 U.S.C. §102(b) as being anticipated by Cruz *et al.* 1990. Cruz *et al.* is cited as disclosing strains of *P. haemolytica* which were modified through a series of internal deletions in the lktA (leukotoxin-A) gene. It is the PTO's position that these strains would inherently have the claimed characteristics and therefore anticipate the claimed invention. Applicants respectfully disagree.

Cruz *et al.* do not disclose a strain of *P. haemolytica* as claimed. Cruz *et al.* did not produce a mutant strain of *P. haemolytica.* Cruz *et al.* only produced a series of internal deletions in an

isolated *P. haemolytica* lktA gene. The isolated and cloned lktA gene was present on plasmid pYFC19. Plasmids derived from the pYFC19 plasmid containing internal deletions of the lktA gene were produced. The *Escherichia coli* strain TB1 served as the host for the plasmids. The deleted forms of the lktA protein were prepared by growing *E. coli* strain TB1 harboring the various plasmids and isolating the expressed lktA protein from the TB1 lysate. The bacteria or that were produced were not derived from the bacterium *Pasteurella haemolytica* but from the bacterium *Escherichia coli*. The microorganism *P. haemolytica* and not the microorganism *E. coli*, is the causative agent of pneumonic pasteurellosis in cattle and is the subject of the rejected claims.

Cruz had no way to move his mutant leukotoxin genes back from *E. coli* into *P. haemolytica* because of the barrier to transformation of *P. haemolytica* which had not yet been overcome in 1990. Thus the best that Cruz could make of his mutant genes in *E. coli* were subunit vaccines. The claims, in contrast, are directed to whole organism vaccines. Few scientists in the field believe that such subunit vaccines would be successful. In any event, Cruz did not make or suggest making a vaccine. Vaccines are, however, the subject of the rejected claims.

Cruz *et al.* neither discloses nor suggest the claimed invention. Reconsideration is requested.

The examiner has cited and relied on the abstract only of the Gentry *et al.* and Cruz *et al.* reference. Submitted herewith, for the examiner's full consideration are the complete Gentry *et al.* and Cruz *et al.* references, as listed on the accompanying form PTO 1449.

In view of the foreign amendment and comments, favorable reconsideration is requested.

Respectfully submitted,

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